Remarks

Claims 1-6, 8, 22, and 24-38 are pending in the subject application. By this Amendment, Applicants have amended claims 1, 2, 6, 25 and 31 to attend to antecedent basis issues and added new claims 39-40. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, Table 2). Entry and consideration of the amendments and new claims presented herein is respectfully requested. Accordingly, claims 1-6, 8, 22, and 24-40 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 102(b) (over Aebersold *et al.*).

Claim 6 is objected to for reciting "affinity-labeled peptide". The Examiner states there is no antecedent basis for this term. In accordance with the Examiner's suggestion, the word "affinity" has been deleted. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1, 6, 25 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. The Office Action argues that claims 1b and 6b recite "the reagent has the general formula A-Y-PRG-" and that the recitation of the general formula renders the claim indefinite since the claim also indicates that the arrangement of A, Y and PRG is interchangeable. Applicants have amended the claim to delete reference to the general formula A-Y-PRG and submit that this issue is now moot.

Claims 25 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the recitation of "PRG group is selected from ---alcohols--- epoxides---" does not further limit the subject matter of the claim from that of the previous claims 24 and 30 since alcohol or epoxide groups are not a sulfhydryl-reactive group, an amine-reactive group or an enzyme substrate. Applicants have amended the dependency of claims 25 and 31 and submit that this issue is now moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 1-6, 8, 22 and 24-38 are rejected under 35 U.S.C. § 103(a) as obvious over Aebersold *et al.* (WO 00/11208) in view of Moutiez *et al.* (1997) and Li *et al.* (1997). The Office Action argues that Aebersold *et al.* teach a method of identification and quantification of a protein in a

sample by cleaving the protein to peptides using a proteolytic enzyme (page 18, paragraph 4) and using a reagent A-L-PRG, wherein A is linked to a solid support (wherein, A comprises biotin, oligohistidine, etc, page 12) and is covalently linked to linker L (L contain metal bound chelate, page 14, 2nd paragraph and may contain a disulfide group, which is cleavable, page 6, last paragraph); PRG comprises a sulfhydryl group, or an enzyme substrate (page 6, 2nd paragraph) N-hydroxysuccinimide ester groups, *etc.* (claim 32 of Aebersold *et al.*) to bind to the cleaved peptides. The Office Action also argues that Aebersold *et al.* teach the use of a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS (FIG 7), peptide sequence information (page 19, 2nd paragraph) combined with isotope tags for qualitative and quantitative analysis of the protein in a sample. Although Aebersold *et al.* teach the use of a linker L being labeled with isotopes, they do not label the proteins with said isotope. Acbersold *et al.* A-L-PRG (similar to applicants' A-Y-PRG) comprises a chelated metal ion and the stable isotope in their L and use the stable isotope as standard in mass spectrometric analysis. However Aebersold *et al.* do not use a reagent A-Y-PRG wherein said reagent is not isotopically labeled and hence does not use metal ion as a standard in mass spectrometric analysis.

The Office Action argues that the use of metal ion as a standard in mass spectrometric studies is well known in the prior art (see page 781, Li *et al.*). Li *et al.* teach a well characterized spectra of peptide bound silver ion in mass spectral analysis (Figure 1, page 783.) It is further argued that the advantage of purifying and detecting proteins using chelated metal tags comprising various metal ions is well known in the art (Porath et al Prot express and Pur. 1992, 3, 263-281, from IDS) using a variety of chelating agents, such as lanthanide metal ions with DOTA (Moutiez *et al.*). Moutiez *et al.* teach a Gd^{3+} ion chelated to DOTA and teach its separation using metal ion chelate affinity chromatography (page 1350 2nd column) and teach that lanthanide metal complex can be detected using luminescence technique (page 1347 2nd column 2nd paragraph).

Therefore, it is argued, that in order to identify and quantify proteins in proteomic samples, one of ordinary skill in the art is motivated to modify the A-L-PRG of Aebersold *et al.* with Gd^{3+} DOTA chelate not being modified by isotope label and use the metal ion as standard (as taught by Li *et al.*) in the method of Aebersold *et al.*, because a peptide sample attached to L-PRG with Gd^{3+} DOTA can be separated by metal ion chelate affinity column by HPLC, and optionally can be

detected by luminescence before passing into the mass spectrometer. As such, the Office Action concludes, it would have been obvious to one of ordinary skill in the art to combine the teaching of Aebersold *et al.*, Moutiez *et al.* and Li *et al.* to make an A-L-PRG regent having Gd^{3-} DOTA complex in L, use it in the method of identification and quantification of proteins in a sample by a tandem technique comprising electrospray ionization mass spectrometry coupled with liquid chromatography (HPLC/ESI-MS/MS (FIG 7), peptide sequence information using Gd metal ion as standard, and optionally detecting the Gd^{3+} DOTA attached polypeptide by using luminescence before passing the sample into the Mass spectrometer. Applicants respectfully disagree.

The Supreme Court has recently observed that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739, 167 L.Ed.2d 705 (2007). The Court also noted, however, that "[a]lthough common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". *Id.* at 1741. The Court of Appeals has also noted that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984).

In this case, the modification to the teachings of Aebersold *et al.* proposed in the Office Action renders the prior art invention unsatisfactory for the analysis of proteins. As noted in the previous response, the present invention differs from the disclosure of Aebersold *et al.* in that the claimed method does not utilize isotopically labeled reagents for the identification of labeled peptides (*i.e.*, the reagent of general formula A-Y-PRG is not isotopically labeled). This differs from the disclosure of Aebersold *et al.* where isotopically labeled reagents are used (see, for example, page 11, first full paragraph and claims 1-19) to identify and/or quantify one or more proteins. Indeed, Aebersold *et al.* specifically encourage the comparison of isotopically heavy and light reagents in the exercise of the disclosure (page 11, second paragraph). Indeed, Aebersold *et al.* indicate (at page 19):

> In this last step, both the quantity and sequence identity of the proteins from which the tagged peptides originated can be determined by automated multistage MS. This is achieved by the operation of the mass spectrometer in a dual mode in which it alternates in successive scans between measuring the relative quantities of peptides eluting from the capillary column and recording the sequence information of selected peptides. Peptides are quantified by measuring in the MS mode the relative signal intensities for pairs of peptide ions of identical sequence that are tagged with the isotopically light or heavy forms of the reagent, respectively, and which therefore differ in mass by the mass differential encoded within the affinity tagged reagent.

Thus, elimination of isotopically labeled reagents would have rendered the methods of Aebersold *et al.* unsuitable for the analysis of proteins and there would have been no motivation to modify the teachings of Aebersold *et al.* as proposed in the Office Action. Thus, it is respectfully submitted that a *prima facie* case of obviousness has not been established by the cited combination of references and reconsideration and withdrawal of the rejection is respectfully requested.

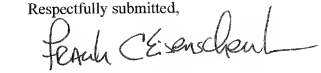
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

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